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The hypoglicemic effects of tapak liman (*Elephantopus scaber L*) plant extract on albino rat (*Rattus novergicus*) models of diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is among the diseases with high morbidity and mortality. The pathogenesis of DM involves pancreatic β-cell damage or insulin sensitivity disorder that result in hyperglycemia. Tapak liman (*Elephantopus scaber L*) is known to have high flavonoid content. Flavonoids are antioxidants that play a role in reducing pancreatic β-cell damage or damage to other tissues, which potentially reduce blood glucose levels.
Objective: To determine the hypoglycemic effects of tapak liman using the DM rat models.
Methods: Twenty-eight Wistar albino rats (Rattus novergicus) were divided into four groups: the normal control group (KKn), not induced by streptozotocin-nicotinamide (STZ-NA) intraperitoneal; negative control group (KK-), induced by STZ-NA; treatment group 1 (KP1), induced by STZ-NA and 150 mg/kg body weight of tapak liman plant extract; and the treatment group 2 (KP2), induced by STZ-NA and 300 mg/kg body weight of tapak liman. Blood glucose levels were measured on the 7th day after STZ-NA induction and the 28th day after the administration of tapak liman plant extract. The results were analyzed for statistical significance.
Results: There was a significant decrease in blood glucose levels in KP1 and KP2 ($p \leq 0.05$). The decrease in blood glucose in KP1 had not reached normal levels compared to KP2.
Conclusion: Administration of tapak liman plant extract at a dose of 300 mg/kg body weight in DM rat models reduced blood glucose levels to normal.

Latar Belakang: *Diabetes melitus (DM) merupakan salah satu penyakit dengan morbiditas dan mortalitas yang cukup tinggi. Patogenesis DM ditandai dengan kerusakan sel β pankreas atau gangguan sensivitas insulin yang menyebabkan naiknya kadar glukosa darah. Tanaman herbal tapak liman (Elephantopus scaber L) diketahui mempunyai kandungan flavonoid yang cukup tinggi. Flavonoid berfungsi sebagai antioksidan untuk mengurangi kerusakan sel β pankreas ataupun jaringan lainnya sehingga berpotensi menurunkan kadar glukosa darah.*
Tujuan: *Penelitian ini bertujuan untuk untuk mengetahui apakah pemberian ekstrak tanaman tapak liman dapat menurunkan kadar glukosa darah puasa tikus putih model DM.*
Metode: *Sampel sebanyak 28 ekor tikus putih (Rattus novergicus) dibagi menjadi 4 kelompok yaitu kelompok kontrol normal (KKn) yang tidak diinduksi streptozotosin-nikotinamid (STZ-NA) intraperitoneal; kelompok kontrol negatif (KK-) yang diinduksi STZ-NA; kelompok perlakuan 1 (KP1) diinduksi STZ-NA dan*

diberi ekstrak tumbuhan tapak liman 150 mg/kgBB; kelompok perlakuan 2 (KP2) diinduksi STZ-NA dan diberi ekstrak tumbuhan tapak liman 300 mg/kgBB. Kadar glukosa darah diperiksa pada hari ke-7 setelah induksi STZ-NA dan pada hari ke 28 setelah pemberian ekstrak tumbuhan tapak liman. Hasil pengukuran kadar glukosa darah selanjutnya diolah secara statistik.

Hasil: *Terdapat penurunan kadar glukosa darah yang signifikan pada KP1 dan KP2 (p≤ 0,05). Namun demikian, penurunan glukosa darah pada KP1 belum mencapai kadar yang normal dibandingkan KP2.*

Kesimpulan: *Pemberian ekstrak tumbuhan tapak liman dosis 300 mg/kgBB pada tikus putih model diabetes melitus dapat menurunkan kadar glukosa darah mencapai normal.*

INTRODUCTION

Diabetes mellitus (DM) is among chronic diseases with high prevalence. In 2015, the global number of individuals with DM reached 415 million and was estimated to increase to 642 million by 2040.[1] In Indonesia, the prevalence continues to rise that in 2017 Indonesia was in the sixth rank of countries with the highest diabetes rates worldwide, reaching approximately 10.3 million DM patients aged 20 - 79 years.[2]

Diabetes mellitus is characterized by hyperglycemia resulting from the damage of pancreatic β-cells thus leading to inability to produce insulin or due to impaired insulin sensitivity in the peripheral tissues thereby inhibiting the cells from making good use of glucose. Hyperglycemia in DM patients will disrupt oxidative processes.[3]

Hyperglycemia can lead to complications in different organs of the human body, including arteriosclerosis, coronary heart disease, and cardiomyopathy in the heart and blood vessels, retinopathy in the eyes, neuropathy in the nerves, as well as nephropathy in the kidneys, all of which can increase morbidity and mortality in DM patients. Therefore, blood glucose levels in patients with DM should be stabilized using medicinal plant therapy among others.[4] In addition to medical treatment, increased blood glucose levels in individuals with diabetes mellitus can be controlled through diet and exercise.[5] Since the side effects of current antidiabetic drugs remain myriad, the development of antidiabetic drugs with minimum side effects continues to be investigated, including studies of potential medicinal plants to control blood glucose levels.[6] Tapak liman (*Elephantopus scaber L.*) is among the medicinal herbs assumed to be capable of reducing blood glucose levels due to its flavonoid content. Flavonoids in tapak liman are luteolin, luteolin-7-Oglucuronide 6"-methyl ester, and luteolin-4-O-β-D glucoside.[7] Flavonoids are plant compounds with the benefit of antioxidant properties that can prevent damage to pancreatic β-cells or other tissues, expectedly leading to reduced blood glucose levels.[8,9]

Research on diabetes mellitus by involving experimental animals as the model has been extensively conducted. The most common compounds used to prepare animal models of diabetes mellitus include streptozotocin (STZ) and nicotinamide (NA) administered through intraperitoneal injection.[10,11] Induction by STZ will increase oxidative stress on pancreatic β-cells, resulting in damage to these cells and failure to produce insulin. In contrast, NA is an antioxidant that protects pancreatic β-cells from the cytotoxic effects of STZ. This model is the most suitable for the antidiabetic activity testing of plant components that are potential for the treatment of type-2 diabetes mellitus.[12]

Therefore, this study aims to identify whether the administration of tapak liman plant extract can reduce the levels of fasting blood glucose in rat models of DM.

METHODS

This study was conducted as a true experimental laboratory design. The ethical clearance obtained from the Ethics Committee of the Faculty of Medicine of Universitas Sebelas Maret No. 693/VII/HREC/2017. The subjects were male albino rats (Wistar strain, Rattus novergicus) aged 2-3 months, weighing 250-280 grams, and having a healthy body and normal

blood glucose levels before the treatment. There were 28 rats taken as the samples randomly divided into four treatment groups, with each group consisting of 7 rats. The experimental design groups comprised the normal control group (KKn), negative control group KK (-), treatment group 1 (KP1), and treatment group 2 (KP2). During the experiment, the rats were provided with standard rat feed and water ad libitum. Before the treatment, the experimental animals were given a period of acclimatization for seven days. Then, three groups (KK (-), KP1, and KP2) were given a single-dose intraperitoneal (IP) injection of STZ 60 mg/kg BW and NA 120 mg/kg BW (NA was administered 15 minutes before STZ) on 8th day to induce diabetes. KP1 and KP2 groups received tapak liman plant extract at a dose of 150 and 300 mg/kgBW, respectively, using a nasogastric tube from day 15 to day 42 (28 days). For all of the rat groups, the blood glucose levels were examined in 3 replications. The first measurement was performed on 8th day (before induction by STZ-NA), the second measurement was on 15th day or 7 days (after induction by STZ-NA) to determine whether the induction of DM was accomplished, and the third measurement was done on 43th day (28 days following the administration of tapak liman plant extract) to determine the effects of the administration of tapak liman plant extract on the treatment groups. The blood glucose levels to be examined were the levels of fasting blood glucose measured through retro-orbital blood sampling. Blood samples were collected in Eppendorff tubes and serum was separated by centrifugation. The serum was used to determine glucose level by the glucose oxidase method. At the end of the experiment, rats were terminated. The differences in blood glucose levels between post-induction by STZ-NA and post-administration of tapak liman plant extract were measured and statistically analyzed using the Paired T-test and Wilcoxon test, whereas the differences in post-treatment fasting blood glucose levels among the groups were analyzed using the Kruskal-Wallis test and Independent T-test.

All of part of tapak liman plant were used to make extract in this study. Tapak liman plants were obtained from CV. Merapi Farma Herbal Yogyakarta in the form of simplicia. The simplicia was extracted using maceration technique with 70% ethanol solvent repeatedly and shaken occasionally. The process was performed for 2 weeks. Once every 2 days, the solvent was replaced and filtered to obtain a liquid extract. The liquid extract was evaporated with a vacuum rotary evaporator to obtain the thick extract. The extraction process was carried out by the staff of the Nutrition Laboratory of the Centre for Food and Nutrition Studies, Universitas Gadjah Mada, Yogyakarta.

RESULTS

Characteristics of Research Subjects

The mean fasting blood glucose levels in all groups (KKn, KK (-), KP1, and KP2) on day 8 after subject acclimatization showed a normal level (<126 mg/dl).

Meanwhile, the mean levels of fasting blood glucose in KKn group on day 8 was approximately the same as that on day 15, whereas in KK (-), KP1, and KP2 groups on day 15 there was a 3-fold increase in blood glucose levels compared to those on day 8. These findings indicated that the administration of streptozotocin-nicotinamide (STZ-NA) on day 8 to the subjects in KK (-), KP1, and KP2 groups could successfully increase the fasting blood glucose levels on day 15, thereby allowing the subjects to become the models of diabetes mellitus. The mean fasting blood glucose levels of the subjects on day 8 and day 15 are presented in Table 1.

Table 1. Mean fasting blood glucose levels on day 8 and day 15

Group	Mean fasting blood glucose level (mg/dl)	
	Day 8	Day 15
KKn	70.53	71.57
KK(-)	72.18	259.55
KP1	73.83	258.49
KP2	72.23	260.25

KKn: normal control group, KK(-): negative control group, KP1: treatment 1 group, KP2: treatment 2 group

Fasting blood glucose levels in the treatment groups after the administration of tapak liman (*Elephantopus scabei L*) extract

On day 43, the fasting blood glucose levels in KKn and KK (-) groups were insignificantly different from those on day 15, although they were statistically significant ($p<0.05$). Meanwhile, there was a decline in the fasting blood glucose levels of KP1 and KP2 groups on day 43, and this decrease was statistically significant ($p<0.05$). However, the fasting blood glucose levels in KP1 group remained above the normal level (>126 mg/dl) while in KP2 group they decreased to below normal. This result has proved that tapak liman plant extract at a dose of 150 mg/kgBW/day administered to KP1 subjects remained ineffective in reducing fasting blood glucose levels when compared to the dose for KP2 group (300 mg/kgBW/day). The mean blood glucose levels of all groups on day 43 are shown in Table 2.

Table 2. Comparison of fasting blood glucose levels among the treatment groups on day 15 and day 43

Group	Mean ± SD of fasting blood glucose level (mg/dl)		p value
	Day 15	Day 43	
KKn	71.57 ± 1.37	74.38 ± 2.13	0.003*
KK(-)	259.55 ± 3.71	261.21 ± 3.68	0.018**
KP1	258.49 ± 2.84	145.75 ± 3.18	0.000*
KP2	260.25 ± 3.14	112.93 ± 3.21	0.000*

*Paired T-test, **Wilcoxon test

The differences in the treatment for KKn, KK (-), KP1, and KP2 groups, which were also statistically significant (examined using the Kruskal-Wallis test), resulted in different fasting blood glucose levels on both day 15 ($p=0.001$) and day 43 ($p=0.000$). On day 43, the fasting blood glucose levels in KP1 and KP2 groups examined using the independent T-test showed a significant difference ($p=0.000$).

DISCUSSION

In the first measurement of blood glucose level, all of the rat groups had normal levels of fasting blood glucose, or below 126 mg/dL, thus allowing all of the acclimatized rats to be involved in the study. The second measurement showed that the rats in the groups induced by STZ-NA, or KK (-), KP1, and KP2 groups, experienced a significant increase in the fasting

blood glucose levels and clinically developed a sign of diabetes mellitus as the fasting blood glucose levels exceeded 126 mg/dL. This indicates that KK (-), KP1, and KP2 can become the groups of rat models of diabetes mellitus. When injected in rats, streptozotocin (STZ, 2-deoxy-2(3-methyl-3-nitrosoureido)-D-glucopyranose), which is a nitrosourea analogue, will be transported to pancreatic β-cells through GLUT2 glucose transporter. In the cells, STZ causes alkylation of DNA, resulting in DNA breakage or DNA damage.[13] Such damage will trigger an increasing activity of poly(ADP-ribose) polymerase-1 (PARP-1) to repair the DNA. PARP-1 enzyme enhances the synthesis of poly (ADP-ribose) from NAD+ leading to a decline in NAD+ and thereby reducing ATP in the cells.[14] Since ATP becomes the source of energy in the cells, its low level will induce necrosis of pancreatic β-cells, thus decreasing insulin synthesis and secretion.[15] Reduced ATP is caused not only by the increasing activity of PARP-1 enzyme but also by mitochondrial dysfunction.[14]

STZ-induced DNA damage to pancreatic β-cells is also caused by the formation of Nitrite Oxide (NO) and Reactive Oxygen Species (ROS) free radicals. Both substances can act independently or simultaneously to form highly toxic peroxynitrite ($ONOO^-$) compounds.[13] ROS is an oxidant from which excessive formation will lead to oxidative stress in the cells, including in the islets of Langerhans of the pancreas.[16] In addition, streptozotocin intensifies the activity of c-Jun N-terminal kinase (JNK), an enzyme that regulates apoptosis, thereby resulting in cell death.[17,18] Injury to and destruction of pancreatic β-cells result in failure to produce insulin.

In contrast, nicotinamide (NA) (pyridine-3-carboxamide), an amide form of vitamin B3 (niacin), is protective toward STZ-induced pancreatic β-cells, and nicotinamide inhibits the activity of PARP-1 enzyme, thereby increasing intracellular NAD^+. Administration of such regimen (STZ and NA) to rats will induce type 2 diabetes mellitus.[14]

Animal models of streptozotocin-induced diabetes mellitus will experience oxidative stress. Oxidative stress represents an imbalance between oxidant and antioxidant substances, and antioxidants are therefore required to combat it.[16] The human body has two types of antioxidant, the enzymatic antioxidant system which includes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxides (GSH-Px), as well as the non-enzymatic antioxidant system.[19] Tapak liman extract can reduce blood glucose levels since it contains several antioxidants, such as flavonoids, phenolic acids and terpenoids.[20,21]

Flavonoids are a potent scavenger of free radicals that act through some mechanisms. Zou et al. (2014) reported the administration of flavonoids which can enhance the activity of SOD antioxidant enzyme. SOD converts superoxide (O_2^-) free radicals into hydrogen peroxide (H_2O_2) which will then turn into the water through an enzymatic reaction mediated by CAT.[22] Another mechanism is through the stabilization of free radicals per se. The hydroxyl groups in flavonoids act as a scavenger by donating hydrogen and electrons to stabilize ROS before the ROS exert their impacts on the body.[9] Flavonoids are structurally composed of two aromatic rings, ring A and ring B, which are connected by three carbon chains that form an oxygenated heterocyclic ring (ring C).[23] The molecular structures of flavonoids that play a significant role in the radical-scavenging activity include B-ring hydroxylation, C2-C3 double bond linked to C3 hydroxyl group and C4 carbonyl group, and A-ring hydroxylation.[24] Flavonoids also act as a potent chelator for prooxidant metal ions, such as Fe^{2+} and Cu^{2+}. The catalyst Fe^{2+} reacts with hydrogen peroxide (H_2O_2) to form hydroxyl radicals, whereas the ion Cu^{2+} reacts with hydrogen peroxide to produce superoxide. The simultaneously produced Cu^+ will then react with excess hydrogen peroxide and form hydroxyl radicals. Flavonoids will eventually form a stable complex along with these metal ions, thereby preventing the formation of ROS.[22,25]

Phenolic acids are another antioxidant with an identical mechanism of action to that of flavonoids, which is to act as a metal ion chelator and ROS scavenger. Phenolic acids primarily stabilize hydroxyl and peroxyl radicals, superoxide anions, and peroxynitrites.[22]

Another antioxidant contained in tapak liman is terpenoids, which can trigger regeneration of pancreatic β-cells damaged by STZ in rat models of DM.[7] The insulin secretory granules of pancreatic β-cells are also increased, thus raising the possibility of insulin production. Besides, terpenoids can act as an agonist/ligand of peroxisome proliferator-activated receptor ɣ (PPARɣ).[26] PPARɣ is a transcription factor that plays a role in controlling glucose and lipid metabolisms, and similar to other nuclear receptors, it is activated by ligand binding. In the pathogenesis of DM, PPARɣ contributes to reducing insulin resistance in the tissues. Therefore, PPARɣ agonist in patients with type-2 diabetes mellitus is used to control blood glucose levels and increase insulin sensitivity.[27] Terpenoids have a relatively high degree of binding affinity for PPARɣ compared to rosiglitazone, an antidiabetic drug that functions as a PPARɣ agonist through molecular docking.[26] Rosiglitazone is no longer used in DM treatment to date due to its numerous side effects.5 In addition to the three compounds previously discussed, tapak liman (*Elephantopus scabei L)* also contains a significant class of steroid, 28Nor-22(R)Witha2,6,23-trienolide, which presumably stimulates pancreatic β-cells to secrete insulin.[8]

Meanwhile, no rats were found dead throughout the course of the treatment, indicating that tapak liman extract at doses of up to 300 mg/kgBW had no toxic effects. This is consistent with the research conducted by Daisy et al. (2009) which found no toxic effects in tapak liman extract observed through the absence of changes in animal behaviour as well as mortality.[8]

The administered dose of tapak liman plant extract also affects the reduction in blood glucose levels. Tapak liman plant extract administered at a dose of 150mg/kgBW (KP1) for 28 days has significantly reduced the fasting blood glucose levels, but this is clinically insufficient to bring the levels back to normal. A normal fasting blood glucose level can only be achieved at a dose of 300 mg/kgBW tapak liman plant extract (KP2 group). Meanwhile, in the study by Daisy et al. (2011), the normal fasting blood glucose levels were achieved only after the administration of tapak liman plant extract at a dose of 250 mg/kgBW for 60 days.[21] Different from this present study, the animal models of diabetes mellitus in Daisy et al. (2011) were induced by STZ alone without NA and the pre-treatment fasting blood glucose levels were significantly higher. Compared to STZ-NA combination, administration of STZ alone in animal models of DM can trigger several side effects, including glucose insensibility, the need for long-term induction, and damage to such organs as liver and kidney.[12]

The method to prepare tapak liman plant extract also affects the plant activity in lowering the fasting blood glucose levels of experimental animals. In this study, tapak liman was extracted using 70% ethanol. Daisy et al. (2011) reported that among the various methods of tapak liman extraction, the one using ethyl acetate, the ester of ethanol and acetic acid, has proved to be the best method to obtain an extract that can reduce fasting blood glucose levels.[21]

CONCLUSION

The administration of tapak liman plant extract at a dose of 300 mg/kgBW to albino rat models of diabetes mellitus can reduce blood glucose levels to normal.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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